Behavioral Disorder, Dementia, Ataxia, and Rigidity in a Large Family With TATA Box-Binding Protein Mutation

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Background: Spinocerebellar ataxia type 17 is an autosomal dominant cerebellar ataxia caused by a CAG repeat expansion in the TATA box-binding protein gene. Ataxia is typically the first sign whereas behavioral symptoms occur later.

Objective: To characterize the unusual phenotypic expression of a large spinocerebellar ataxia type 17 kindred.

Design: Clinical, neuropathological, and molecular genetic characterization of a 4-generation family with 16 affected patients.

Results: Behavioral symptoms and frontal impairment dominated the early stages preceding ataxia, rigidity, and dystonic movements. Neuropathological examination showed cortical, subcortical, and cerebellar atrophy. Purkinje cell loss and gliosis, pseudohypertrophic degeneration of the inferior olive, marked neuronal loss and gliosis in the caudate nucleus, and in the medial thalamic nuclei were salient features together with neuronal intranuclear inclusions stained with anti–TATA box-binding protein and antipolyglutamine antibodies. The disease was caused by a stable 52 CAG repeat expansion of the TATA box-binding protein gene, although there was apparent variability in the age of onset.

Conclusion: The characteristics of this family broaden the clinical picture of spinocerebellar ataxia type 17: initial presenile dementia with behavioral symptoms should be added to ataxia, rigidity, and dystonic movements, which are more commonly encountered.

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stained with hematoxylin-eosin, Masson trichrome stain, periodic–acid Schiff, and Bodian silver stain coupled with Luxol fast blue. Immunohistochemistry was performed as previously described, with the following antibodies: antiubiquitin (dilution 1:1000; Dako, Tokyo, Japan), anti-TBP (dilution 1:500; Santa Cruz Biotechnology, Santa Cruz, Calif), and antipolyglutamine 1C2 (dilution 1:4000; Immunochem Diagnostic Technologies Ltd, Truro, Nova Scotia). Neuronal loss and gliosis were semiquantitatively assessed. The percentage of neuronal nuclei, which bore neuronal intranuclear inclusions (NIIs) or were diffusely labeled, was evaluated on a sample of 100 nuclei, when possible. Comparisons between these values were performed with an analysis of variance. The protected least significant difference of Fisher was used to compare the prevalence of NIIs and of diffuse 1C2 labeling of the nuclei in regions with no, mild, moderate, or severe neuronal loss.

MOLECULAR ANALYSIS

Lymphoblasts from patients 7 and 30, from 14 negative controls, and from 2 positive controls (SCA3) were solubilized by standard methods. Protein samples were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Antipolyglutamine monoclonal antibody 1C2 (dilution 1:2000; Euromedex, Souffelweyersheim, France), 1F8 (dilution 1:5000), and anti-TBP monoclonal antibody 3G3 (dilution 1:3000) were used. We examined 10 affected, 2 at-risk, and 6 healthy individuals belonging to the family, 50 unrelated healthy controls, and 30 disease controls whose phenotype included hereditary spinocerebellar degeneration, mental retardation, seizures, and essential tremors.

The stretch of the TBP gene containing the CAG/CAA repeat was amplified by polymerase chain reaction under conditions previously described. Polymerase chain reaction products were subcloned into pGEM-T easy vector (Promega, Seattle, Wash) and sequenced using the DYEnamic ET Dye Terminator Cycle Sequencing kit on a MEGABACE 1000 automated sequencer (Amersham Pharmacia, Piscataway, NJ).

RESULTS

The family comprises 230 members across 5 generations, among whom 16 individuals were affected (4 men and 12 women) (Figure 1). Mean ± SD age at onset was 33.3 ± 10 years (range, 17-53 years); mean ± SD age at death for 8 patients was 54.6 ± 7.3 years (range, 48-69 years) after a disease duration of 23.8 ± 6.7 years (range, 13-30 years). Mean ± SD age at onset was 39 ± 1.3 years for generation 3, 33 ± 12 years for generation 4, and 24 ± 7 years for generation 5. Table 1 reports early and late behavioral abnormalities for 13 of 16 patients.

CLINICAL OUTLINE OF CASE 7

At age 17 years, the patient experienced the onset of behavioral abnormalities: nervousness, neglect of personal hygiene, and inability to plan or perform basic tasks. At age 20 years, she neglected her children (eg, failed to feed them); she experienced a lack of concern and was

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Abbreviation: NA, not applicable.

Table 1. Behavioral Details

Figure 1. Simplified pedigree without the branches of the family with unaffected parents. Closed squares indicate affected men; closed circles, affected women; open squares or circles, unaffected individuals; and slashes, deceased.
homeless, wandering in towns, sleeping in stations, and begging for cigarettes. At 32 years of age, the patient experienced the onset of neurological signs: hand tremors and a difficulty in gait and speech. At age 35 years, she had an unsteady, broad-based, ataxic, and rigid gait; she also had dysarthria and a marked reduction of verbal fluency. She appeared to have dementia and was temporally disoriented, showing a lack of insight, having a fatuous expression, and experiencing a crisis of laughing and crying.

At age 39 years, the patient was disoriented in space and time (Short Portable Mental Status Questionnaire, a score of 2 of a possible 10), had memory impairment (Corsi span, 0; verbal span, 2 for both numbers and words; delayed memory, 3.5/21; Babcock story, 3.3/16), and was unable to learn new information (Wechsler Adult Intelligence Scale IQ, verbal score, 54; IQ performance score, 44; IQ total, 47). She had constructional apraxia (0/14), orofacial apraxia (3/20), and frontal lobe involvement (Raven color matrices, 11/36). Ideomotor apraxia was absent, and her language was severely altered. Electroencephalogram was diffusely slowed, visual and central motor-evoked potentials were normal, and late components of the brainstem evoked potentials were absent. Magnetic resonance imaging revealed global atrophy of the cerebral and cerebellar cortices.

At age 42 years, she was wheelchair bound and had unintelligible speech, incontinence, and impressive axial and limb rigidity, but no Babinski sign. She also had slow eye and dystonic arm movements, myoclonus, and epileptic seizures. Although completely mute, she understood and recognized the examiner. At age 44 years, she was bedridden, had difficulties in swallowing, was cachectic with massive muscle atrophy (no fasciculations), and experienced flexor rigidity in 4 limbs. She died at age 48 years.

**NEUROPATHOLOGY AND IMMUNOHISTOCHEMISTRY OF CASE 7**

The patient's brain was small and weighed 600 g. Atrophy was diffuse, involving all brain regions; atrophy of the cerebellum was the most severe. A microvascular change, at the convexity of the gyri, was found in layer 2 of the cerebral cortex, predominating in the frontal areas. Neuronal loss and gliosis were absent or minimal, except in the motor cortex and in the primary visual cortex. The secondary visual areas showed a marked gliosis. Hippocampus appeared normal. In the striatum, neuronal loss was severe; astrocytosis was prominent. The nucleus accumbens, the anterior part of the putamen, the pallidum, and the claustrum appeared normal, as did the nucleus basalis of Meynert and the hypothalamus. Within the thalamus, the dorsomedial nucleus was severely affected, with near-total nerve cell loss and severe gliosis. Similar changes were observed in the nuclei ventro-oralis internus and, markedly, in the nuclei medial to the mammillothalamic tract (nucleus reuniens and nucleus ventralis medialis anterior). In contrast, the lateral (centrolateral and dorsolateral nuclei) and basal parts of the thalamus, as well as the anterior nucleus, did not show nerve cell loss or gliosis. The subthalamic nucleus was normal. The centrum semiovale was pale. In the mesencephalon, nerve cell loss in the substantia nigra was mild; there were a few deposits of free melamin pigment without Lewy bodies. The tegmentum was normal. There was a severe atrophy of the crus cerebri predominating in the medial two thirds, with a relative sparing of the density of the myelinated fibers. Loss of nerve fiber and astrocytosis were observed in the descending tracts of the pons. The pontine nuclei appeared normal. Neuronal loss was severe in the inferior olive, which appeared hypertrophic and gliotic. Pyramids were shrunken and gliotic. In the cerebellum, the density of Purkinje cells was low. Bergmann glia was prominent. The molecular layer was thin. Neuronal loss and gliosis were mild in the granular layer. Fiber loss and astrocytosis were severe in the cerebellar white matter. Neuronal loss was moderate in the dentate nucleus; the cell body of the spared neurons appeared shrunken and hyperchromatic; the fleeces of the nucleus and its hilum were severely gliotic. In the spinal cord, there was a slight pallor of the anterolateral tracts. Posterior columns and anterior horn were normal.

**IMMUNOHISTOCHEMISTRY**

Neuronal intranuclear inclusions were immunolabeled by antiubiquitin, anti-TBP, and 1C2 (Figure 2E-G). They were infrequent, affecting on average 0.5% of the total number of neuronal nuclei, and they were widely distributed within the central nervous system, even in apparently unaffected regions (Table 2). Their frequency was significantly higher (1.3%) in the areas with a moderate neuronal loss (F = 3.53; P < 0.05) than in regions with no, mild, or severe loss. Nuclei of some neurons were diffusely stained with 1C2 (Figure 2H). The frequency of diffusely labeled nuclei was quantitatively assessed. It was low in areas with no (3.6% ± 1.8%) or, on the contrary, severe (1.2% ± 1.2%) neuronal loss. Their frequency was high (mild, 20.2% ± 7.5%; moderate, 29% ± 8.8%) in regions where the neuronal loss was estimated to be of intermediate severity (mild or moderate). Differences were statistically significant (protected least significant difference: between mild and unaffected, P < 0.03; mild and severe, P < 0.04; moderate and unaffected, P < 0.02; moderate and severe, P < 0.03). There was no correlation between the frequencies of diffuse neuronal staining and those of NII (r = 0.24; P > 0.05). The neuropathological findings are summarized in Table 2.

**MOLECULAR GENETIC RESULTS**

All affected and at-risk members carried 52 CAG/CAA repeats in the expanded allele, corresponding to the approximately 47.5-kDa band in patients 7 and 30 (Figure 3). Sequence analysis performed on patients 7 and 30 confirmed the number of repeats with the following structure of the repeat region: (CAG)3 (CAA)3 (CAG)9 CAA CAG CAA (CAG)32 CAA CAG.

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The family has a fairly homogeneous, although complex, clinical picture, characterized by early and prominent behavioral disorder that, together with the strong reduction of verbal fluency, is followed by a definite picture of frontal lobe dementia. Apraxia and agnosia were not features of this dementia. Cerebellar signs were noticed later but were eventually masked by extrapyramidal signs such as dystonia and rigidity. Myoclonus and
epilepsy were characteristic of the late stages of the disease. The main neuropathological characteristics of the autopsied case were a low brain weight; atrophy of the frontotemporal cortex; nerve cell loss in the precentral gyrus, the primary visual cortex, the striatum, and the thalamic dorsomedial nucleus; pseudohypertrophic degeneration of the inferior olive; and severe loss of Purkinje cells. Immunolabeling for ubiquitin, TBP, and 1C2 revealed diffuse nuclear reactivity and NIIIs. The frequency of NIIIs was low in the areas where the neuronal loss was severe, perhaps because the NII-bearing cells died. It was also low when the neuronal density was considered normal, suggesting that neurons devoid of NIIIs were spared. Finally, there was a link between diffuse labeling of the nuclei and neuronal loss, raising the possibility that the mutated protein may have had a toxic effect in the nucleus even in the absence of NII formation.

Atrophy or hypoplasia could be responsible for the low brain weight (600 g). A developmental alteration leading to hypoplasia has been advocated in SCA2 and dentatorubral-pallidoluysian atrophy;\textsuperscript{18} and TBP could play a role in the development.\textsuperscript{19} The protracted course of the disease could explain, on the other hand, a severe atrophy.\textsuperscript{20} Clinicopathological correlation is difficult to analyze in a disorder that diffusely affects the brain. Nevertheless, alterations of the frontal lobe, thalamic nuclei projecting to it, cerebellum, and caudate nucleus could be held responsible for the behavioral difficulties and the cognitive deficit. The cerebrocerebellar circuitry is an obvious candidate pathway when considering an anatomical basis for cerebellar-cognitive interactions.\textsuperscript{21} Feedback circuits relaying in the thalamus project to the same cortical areas from which the cerebellum receives its afferent inputs. A syndrome consisting of behavioral disorder, linguistic difficulties, disturbances of executive functions, and impaired spatial cognition has been already described in patients affected by diseases confined to the cerebellum.\textsuperscript{22}

Neuronal loss in the caudate nucleus probably explains similarities between this case and patients with Huntington disease, such as dystonia and dementia. Pyramidal tract degeneration and the rigidity associated with it may be ascribed to the elective involvement of the primary motor cortex, in the absence of motor neuron disease. The cerebellar symptoms are correlated with the nearly complete loss of Purkinje cells. The pseudohypertrophic degeneration of the inferior olives is secondary to the massive cerebellar lesions; the sparing of the tracts tegmentalis centralis may be correlated with the absence of velopalatar myoclonus, contrasting with the presence of skeletal myoclonus.

The disease is dominant and due to a mutation in the SCA17 gene. The age of onset, ranging from 17 to 53 years, does not correlate with the number of CAG repeats, as previously shown in SCA17\textsuperscript{23} and in other SCAs.
affected subjects had a stable 52 TBP CAG repeat expansion, despite the reported differences in the age of onset among generations 3, 4, and 5. Difficulties in determining the initial symptoms, affecting behavior and mood, are related to patients' lack of insight, as in frontotemporal dementia.23 Heterogeneity of the age of onset may just be apparent.

Major differences were noticed between cases from this family and previously reported cases. Clinically, the disease progressed slowly, lasting approximately 30 years, a course that appears longer than in other families.7,12 In this family, the disease started with behavioral problems, whereas ataxia was predominant at onset in all SCA17 patients.5,11,12 Behavioral symptoms (paranoia, violent behavior, and hypersexuality) were also noticed in Belgian patients12 who had visual hallucinations in the advanced stages. Although epilepsy was present,5,12 myoclonus had not been previously reported. From a neuropathological point of view, brain weight was not so markedly decreased in the other SCA17 cases.12 The caudate nucleus was often reported as normal13 but showed moderate cell loss and gliosis in a Japanese patient who had dystonia.3 These differences suggest that closely linked modifying genes might interfere with the mutated TBP and profoundly alter the phenotype.

Finally, the similarities of the symptoms and of the lesions among cases bearing CAG mutations on different genes should be stressed. In most CAG expansion diseases, cerebellar alterations are present. In several, cognitive impairment has been mentioned: SCA1,1 dentatorubral-pallidoluysian atrophy,4 SCA2, SCA12,3 and, less often, SCA3.4 The cognitive impairment profile showed by Burk et al’s patients is similar to that of our cases and corresponds to the frontal-subcortical dementia in which executive functions are more compromised when compared with visuospatial memory tests. In Huntington disease, the atrophy of the caudate nucleus is the predominant lesion, which is also found in the SCA17 case that we describe. These data suggest that CAG expansions could have common deleterious effects, whatever the mutated gene. Spinocerebellar ataxia type 17 should be considered when behavior abnormalities and frontal-subcortical dementia are associated with ataxia and involuntary movements in presenile patients with a familial history of behavioral dementia and ataxia.

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Figure 3. Western blot analysis of lymphoblasts. A, Wild-type TATA box-binding protein, approximately 37-kDa band (patients 7, 30); expanded TATA box-binding protein, approximately 47.5-kDa band; and expanded ataxin 3 (positive controls): approximately 63-kDa band. B, Absence of approximately 63-kDa band (ataxin 3). C, indicates negative controls; MoAb, monoclonal antibody; SCA3, spinocerebellar ataxia type 3.

REFERENCES


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